

### Remarks/Arguments

The cancellation of claims 20-29, 34 and 37 renders moot all rejections of these claims.

Claims 30-33, 35, 36, 38 and 39 are pending in this application.

Claim 30 was rejected under 35 USC 103(a) over Longley et al in view of Goekjian et al in further view of Ma et al. Applicants request reconsideration and withdrawal of this rejection for the reasons that follow.

The amendment to claim 30 incorporates the limitation of now cancelled claim 34. Thus, the mastocytosis to be treated with midostaurin (PKC412) is resistant to imatinib and is characterized by KIT tyrosine kinase receptor with a D816V mutation. Applicants assert that the rejection under 35 USC 103 is not proper because the Examiner has not established that there had been a finite number of identified, predictable potential solutions to the problem solved by the present invention, the prior art would not lead the skilled artisan to have a reasonable expectation of success and because the present invention solves a long felt but unsolved need.

Longley et al is relied on as disclosing that activating c-kit mutations are necessary, if not sufficient for some forms of mastocytosis and as teaching that inhibiting activated kit with kit inhibitors might be therapeutically useful in mastocytosis. Goekjian et al is relied on as teaching that midostaurin is a broad range kinase inhibitor that has been found to inhibit c-kit at approximately micromolar concentration. Ma et al is relied upon as teaching that adult-type or sporadic adult-type mastocytosis is characterized by mutations in c-kit codon 816 and particularly D816V mutant kit. Ma et al is also relied upon as demonstrating that mast cell lines with EST mutations were not inhibited by imatinib (STI571) suggesting that certain mastocytosis is resistant to imatinib.

In the response filed August 6, 2009, Applicants argued that such a disclosure merely provides a theoretical basis to experiment with kit inhibitors for the treatment of mastocytosis. In support of this position, Applicants pointed out that the experiments described in Longley et al demonstrate that the kit inhibitors tested had variable activity against canine P-815 c-kit, which is taught to correspond to the human D816V mutation that causes constitutive receptor activation in most cases of adult mastocytosis. Of the five indolinone kit inhibitors of wild-type kit tested by Longley et al, only one, SU6577, at a concentration of 40  $\mu$ M, could substantially inhibit constitutive

kit phosphorylation in the P-815 cell line. The caption under Figure 2 discloses that only SU4984 and SU6577 kill P-815 cells. At page 693, the reference further discusses the variable activity against the activating mutations included in the experiment. Therefore, Applicants argued, Longley et al would lead the skilled artisan to try to identify inhibitors of the D816V mutant kit and would not lead the skilled artisan to generally expect inhibitors of wild-type kit to provide a therapeutic benefit in mastocytosis.

Applicants further pointed out although Goekjian et al discloses that midostaurin is an inhibitor of wild-type kit, none of the references disclose that midostaurin effectively inhibits the D816V mutant kit associated with mastocytosis. Therefore, Applicants argued that the combined disclosure of the references would not lead the skilled artisan to have a reasonable expectation of success with respect to midostaurin's potential for treating mastocytosis, especially mastocytosis that is resistant to imatinib and has KIT tyrosine kinase receptor with a D816V mutation.

The Examiner relies upon an 'obvious to try' standard for maintaining the rejection, concluding:

Thus, to one of ordinary skill in the art at the time of the invention would have found it **obvious to try** the midostaurin of Longley et al in sporadic adult-type mastocytosis since Goekjian teaches that midostaurin is a potent inhibitor of c-kit with low toxicity properties. Given the teachings of Longley, Goekjian, and Ma, one of ordinary skill would have been **motivated to try** midostaurin in light of the disclosures of Goekjian, Longley and Ma with the reasonable expectation of providing a method effective in treating sporadic adult type mastocytosis and imatinib-resistant mastocytosis with a potent and low toxicity Staurosporine derivative. (emphasis added)

In response, Applicants assert that the Examiner is relying on an improper legal standard for rejecting the present claims. Applicants particularly rely MPEP 2143(E) and the Federal Circuit's opinion in In Bayer Schering Pharma AG v. Barr Laboratories, 575 F.3d 1341; 2009 U.S. App. LEXIS 17372; 91 U.S.P.Q.2D 1569 (Fed. Cir. 2009), and the case law cited therein, both of which provide guidance about the application an 'obvious to try' standard to reject claims in unpredictable arts. Applicants assert that the present rejections under 35 USC 103 are improper based on the standards set forth in MPEP and Bayer v. Barr because what was 'obvious to try' according to the Examiner was merely to explore the general approach of testing kit inhibitors in mastocytosis without any indication or suggestion that, of all the possible choices, midostaurin would possess the desired properties.

MPEP 2143(E) sets forth the Examiner's burden, according to the USPTO, to properly reject claims based on an 'obvious to try' standard:

**E. "Obvious To Try" - Choosing From a Finite Number of Identified, Predictable Solutions, With a Reasonable Expectation of Success**

To reject a claim based on this rationale, Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:

- (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
- (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
- (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
- (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Applicants assert that the present rejection does not satisfy requirements (2) and (3) of the MPEP:

There are numerous compounds identified as kit kinase inhibitors in the cited references and there are undoubtedly many more kit inhibitors known in the art. On this basis alone, there are not a finite number of identified possible solutions. However, the references also provide information that would lead the skilled artisan to expect that many (if not most) of these kit inhibiting compounds would not provide a therapeutic benefit against mastocytosis that is resistant to imatinib and has KIT tyrosine kinase receptor with a D816V mutation. Therefore, it is clear that there are a large number of unpredictable solutions, rather than a finite number of identified, predictable solutions, as is required according to MPEP 2143(e)(2).

Moreover, it is clear from the cited references that many of the kit inhibitors tested yielded results that lead to the conclusion that they would not be therapeutically effective against mastocytosis that is resistant to imatinib and has KIT tyrosine kinase receptor with a D816V mutation. It is clear that activity against D816V mutant kit is expected to be required in order to obtain such a therapeutic benefit. Since none of the cited references disclose that midostaurin has activity against the D816V mutant, there is no basis for the skilled artisan to have a reasonable expectation of success, as is required according to MPEP 2143(e)(3).

Applicants' position is further supported by the Federal Circuit's opinion in Bayer v. Barr:

In KSR, the Supreme Court stated that an invention may be found obvious if it would have been obvious to a person having ordinary skill to try a course of conduct:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. This approach is consistent with our methodology in *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). See *Procter & Gamble Co. v Teva Pharms. USA, Inc.*, 566 F.3d 989, 996-97 (Fed. Cir. 2009); *In re Kubin*, 561 F.3d 1351, 1359, (Fed. Cir. 2009). *O'Farrell* observed that most inventions that are obvious were also obvious to try, but found two classes where that rule of thumb did not obtain.

First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *O'Farrell*, 853 F.2d at 903. This is another way to express the KSR prong requiring the field of search to be among a "finite number of identified" solutions. 550 U.S. at 421; see also *Procter & Gamble*, 566 F.3d at 996; *Kubin*, 561 F.3d at 1359. It is also consistent with our interpretation that KSR requires the number of options to be "small or easily traversed." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903. This expresses the same idea as the KSR requirement that the identified solutions be "predictable." 550 U.S. at 421; see also *Procter & Gamble*, 566 F.3d at 996-97; *Kubin*, 561 F.3d at 1359-60.

Applicants assert that the disclosures of Longley et al and Ma et al would not lead the skilled artisan reasonably expect for kit inhibitors to be generally useful for treating mastocytosis that is imatinib resistant and has KIT tyrosine kinase receptor with a D816V mutation. Indeed, these references clearly lead the skilled artisan to expect only kit inhibitors which inhibit the D816V mutant to have the potential for therapeutic utility in this condition. The references further provide

information that would lead the skilled artisan to conclude that many, if not most, kit inhibitors do not inhibit D816V mutant kit. Therefore, at best, the combined disclosure of Longley et al and Ma et al suggest the general approach of testing kit inhibitors to determine whether they have utility. However, without some disclosure that would lead the skilled artisan to expect midostaurin to inhibit D816V mutant kit, it is clear that the presently claimed invention falls into the classes of invention where what was 'obvious to try' is nevertheless patentable under the case law discussed in Bayer v. Barr. Therefore, Applicants assert that present rejection is improper and should be withdrawn.

Applicants note that the decision in Bayer v. Barr affirmed a district court ruling of obviousness. However, the decision was based on the determination that the prior art funneled the skilled artisan to two known, predictable solutions to the problem at hand, formulating drospirenone. Additionally, the court held that the prior art did not merely point toward a general approach or area of exploration, but rather guided the formulator directly to the two choices, each of which was reasonably expected to work. The dissent would have found the invention nonobvious. The present circumstances are different because the cited references are relied on for merely suggesting an area of exploration and provide no information that would lead to midostaurin from the myriad of possibilities.

Although Applicants assert that the present claims are patentable for the reasons discussed above, Applicants further assert that the presently claimed invention is patentable because it fills a long felt but unsolved need. See, Graham v. John Deere Co., 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966).

Longley et al discloses the need for effective treatments for mastocytosis. See, page 689-690 and 694. This view is confirmed by Gotlib et al and Gleixner et al, both which are of record, having been submitted with the Amendment of August 8, 2009. Therefore, Applicants assert that the present invention fulfills a long felt but unmet need and that this secondary indicia of nonobviousness further demonstrates the patentability of the present invention. Applicants further point out that Gotlib et al report the generally positive response seen in a clinical trial where a single patient suffering from mastocytosis with the D816V mutation was treated with midostaurin.

Applicants request withdrawal of the rejection of claim 30 under 35 USC 103(a) for the reasons discussed above.

Applicants further request reconsideration and withdrawal of the rejections of claims 31-33, 35, 36, 38 and 39 under 35 USC 103(a) for the same reasons as discussed above with respect to claim 30.

Entry of this amendment and reconsideration and allowance of the claims are respectfully requested.

Respectfully submitted,

A handwritten signature in dark ink, appearing to read "George Dohmann", is written over a horizontal line.

George Dohmann  
Attorney for Applicant  
Reg. No. 33,593

Novartis Pharmaceuticals Corporation  
One Health Plaza, Bldg. 101  
East Hanover, NJ 07936  
(862) 778-7824

Date: April 16, 2010